C-11 Choline PET/CT Imaging for Differentiating Malignant From Benign Prostate Lesions

Xin Li, MD, Qi Liu, MD, PhD,* Muwen Wang, MD, PhD,*† Xunbo Jin, MD,* Qingwei Liu, MD, PhD,* Shuzhan Yao, MD,* Songtao Liu, MD,* and Jun Li, MD**

Purpose: To investigate the potential of C-11 choline PET/CT imaging for differentiating prostate cancer (PCa) from benign prostate hyperplasia (BPH).

Materials and Methods: Forty-nine patients with prostate lesions underwent C-11 choline PET/CT imaging that was performed 5 minutes after injection of 7.4 MBq/kg (0.2 mCi/kg C-11 choline in the supine position over 2 bed positions (3 minutes per position), covering the pelvis, and the whole body (6 bed) when necessary. After attenuation correction, PET data were analyzed visually and semiquantitatively by measuring maximum standardized uptake value (SUVmax) of the prostate lesions (target) and the muscles (nontarget) and calculating their ratios (P/M).

Results: Twenty-one PCa and 28 BPH lesions were proven histologically. The mean values of the SUVmax of PCa and BPH were 7.87 ± 5.74 and 4.95 ± 5.14, respectively without a significant difference between these 2 groups ($t = 2.02$; $P > 0.05$). The mean P/M of PCa and BPH were 4.21 ± 1.61 and 1.87 ± 0.98. The statistical difference of P/M between them was significant ($t = 2.04$; $P < 0.01$). Using 2.3 (P/M) as the criterion, C-11 choline PET/CT imaging showed a sensitivity of 90.48%, a specificity of 85.71%, and a negative predictive value of 92.31%. PET/CT precise localization of the hot spot in different parts of the prostate could contribute to the diagnosis.

Conclusions: C-11 choline PET/CT is a valuable noninvasive imaging technology in the diagnosis of PCa. The parameter P/M could differentiate PCa from benign lesions better than SUV.

Key Words: prostate carcinoma, C-11 choline, PET/CT

(*Clin Nucl Med* 2008;33: 671–676)

Early detection of prostate cancer (PCa) may feasibly lead to an increased cure rate. The accuracy of clinical examination, ultrasonography, and current radiographic techniques for detecting localized, curable PCa is limited, and an accurate, noninvasive imaging method to visualize PCa is needed.

F-18 FDG PET has been shown to be an accurate technique for tumor detection in most malignant tumors. But it is limited in detecting PCa for 2 reasons; the low uptake of FDG in PCa and the rapid excretion of FDG in urine, causing an accumulation of activity in the bladder.

C-11 choline has recently been reported as an appropriate probe for noninvasive imaging of PCa deposits in patients.[1,2] Choline is necessary in the human body for phospholipid synthesis in cell membranes, transmembrane signaling, and lipid cholesterol metabolism and transport.[3] It is transported into cells, phosphorylated, and thus trapped within the cells and used for synthesis of phospholipids. Malignant tumors may show up-regulated key enzymes of choline metabolism[4,5] and increased metabolism of cell membrane components, which will lead to an increased uptake of choline.[6,7]To date, no agreement exists as to the value of PET in localization of early PCa, and recent reports on this issue have been contradictory.[8,9] Some authors postulated a significant overlap in uptake values of C-11 choline between PCa and benign prostate hyperplasia (BPH),[7] whereas others demonstrated that C-11 choline PET was effective in revealing PCa within the gland.[2] Using PET in conjunction with computerized tomography (PET/CT) may enhance localization of sites of C-11 choline accumulation. Therefore, the aim of this study was to investigate the potential of C-11 choline PET/CT imaging for differentiating PCa from BPH.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the PET/CT results of 49 patients (mean age, 70.6 years; range, 48–92 years; mean preoperative prostate-specific antigen (PSA) level, 24.5 ng/mL; range, 1.1–100 ng/mL) who had prostate disease and underwent C-11 choline PET/CT imaging before transrectal needle biopsy between April 2004 and January 2006 at our center. Those patients who had received antiandrogen therapy were not included in this study. Of 49 patients, 35 cases were verified by operative specimens assessment, and 14 were verified by transrectal needle biopsy with at least 10 months follow-up (Table 1).

Received for publication August 8, 2007; revision accepted March 5, 2008.
From the *PET/CT Center, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, China; and †James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.
This work was funded in part by the Science and Technology Progress Project of Shandong Province (2004GG2202140) and the National Natural Science Foundation of China (30670581).
Reprints: Qingwei Liu, MD, PhD or Qi Liu, MD, PhD, PET/CT Center, Provincial Hospital Affiliated to Shandong University, Shandong University, Jingwu Road 324#, Jinan City, Shandong Province, 250021, China. E-mail: docyyx@163.com or doclx@sina.com.

ISSN: 0363-9762/08/3310-0671

TABLE 1. Patient Characteristics

Characteristic	Value
Age(y)	
Mean	70.64
Range	48–92
Serum PSA	
Mean	24.51
Range	1.1–100
Patients with prostate cancer (21) Gleason score	
Mean	6.2
Range	4–9
Clinical stage (Jewett)	
A2	2
B1	3
B2	8
C1	0
C2	1
C3	1
D1	4
D2	2

C-11 Choline PET/CT

C-11-O_2 was produced by a Minitrace cyclotron (GE Healthcare). C-11 choline was synthesized according to the solid-phase method in a modified commercial synthesis module (TRACERlab FXc; GE Healthcare).

All PET scans were obtained with a dedicated PET/CT scanner (Discovery LS; GE Healthcare). After a rest, patients drank 1 liter of water to make the bladders full a half-hour before examination without fasting. Five minutes after intravenous injection of 7.4 MBq/kg (0.2 mCi/kg) of C-11 choline, PET images were acquired in the supine position over 2 bed positions (3 minutes per position) from the upper pelvis through the mid thigh. For patients with a PSA >10 ng/mL, whole body PET/CT imaging was performed (6 bed positions). The parameters of the multidetector helical CT scan were 140 kV, 80 mA, 0.8 seconds per tube rotation, slice thickness of 5 mm, pitch of 6, and table speed of 11.25 mm/s. PET images were reconstructed with the iterative reconstruction ordered-subset expectation maximization likelihood algorithm of the manufacturer after attenuation correction based on the CT dataset. Consecutive transverse PET/CT slices of 4.25-mm thickness were generated.

Image Analysis

All PET images were analyzed with dedicated software (Xeleris; GE Healthcare) that allowed review of PET, CT, and fused-image data. PET images were first assessed visually, using transaxial, sagittal, and coronal displays by 2 experienced nuclear medicine physicians who were unaware of the clinical data and results of previous imaging studies. To determine the exact location of focal uptake, CT images and integrated PET/CT system were used to decide whether the prostate lesion was located in the peripheral zone or in the central zone. Afterwards, a circular region of interest (ROI) of the abnormal focus of increased C-11 choline uptake in the prostate gland was drawn and the maximum standardized uptake value (SUVmax) was measured. We also drew at least 3 circular (1 cm in diameter) ROI in the pelvic muscles at the same slice as the prostate lesions, and the highest SUVmax was accepted as the SUVmax of the muscles. The radioactivity concentrations of the prostate lesions (target) and the muscles (nontarget) were measured and their ratios (P/M) were calculated. The PET/CT findings were compared with histopathologic results.

Because of the limited spatial resolution of PET/CT and potential movements of the prostate between CT and PET acquisition, we did not try to determine capsular invasion.

Statistical Analysis

Data were compared by independent samples t test or nonparametric tests (2-independent samples tests). The receiver operating characteristic (ROC) analysis was performed by calculating the sensitivity and specificity for a sample of threshold value of P/M using SPSS software (version 13.0). Two-tailed $P < 0.05$ was considered significant.

RESULTS

Histopathological Results

Twenty-one patients were proven to have PCa pathologically including 5 well-differentiated, 7 moderately differentiated, and 9 poorly differentiated adenocarcinomas. Seven PCa patients had a Gleason grade ≥4 (38.9%), and 6 patients were no less than C stage (Jewett modified method). Six patients were found with lymph nodes and/or bone metastases. In the remaining 28 patients, histology resulted in a diagnosis of BPH including 8 patients who also had chronic prostatitis.

C-11 Choline PET/CT Imaging

Characteristics of C-11 Choline PET/CT Imaging

All PCa cases could be visualized as avid accumulation of C-11 choline in the gland. Among 21 PCa cases, diffuse accumulation of radioactivity in the entire prostate gland was observed (Fig. 1) in 15 patients, and a solitary hot spot within the peripheral zone of the prostate gland was visualized (Fig. 2) in 6 patients. Among 28 benign diseases, symmetrically high uptake of C-11 choline within the central zone of the prostate (Fig. 3) was noted in 22 BPH cases and only 1 case could be visualized as the accumulation of radioactivity in the peripheral zone. The remaining 5 BPH cases showed little accumulation of radioactivity in the prostate.

PET/CT also revealed lymph node and/or bone metastases with clear focal accumulation of C-11 choline in all 6 patients (known from bone scintigraphy, MRI or CT) (Fig. 4).

Semiquantitative Analysis

Using SUV as a Semiquantitative Parameter. In PCa, the mean values and ranges of the SUVmean were 7.25 ± 4.98 (1.58–25.28), whereas in BPH, the mean SUVmean was 4.51 ± 4.74 (0.67–26.19). No statistically significant difference was found between them ($t = 2.02$; $P > 0.05$). The mean values of SUVmax of the PCa and BPH were 7.87 ± 5.74 (2.75–27.85)

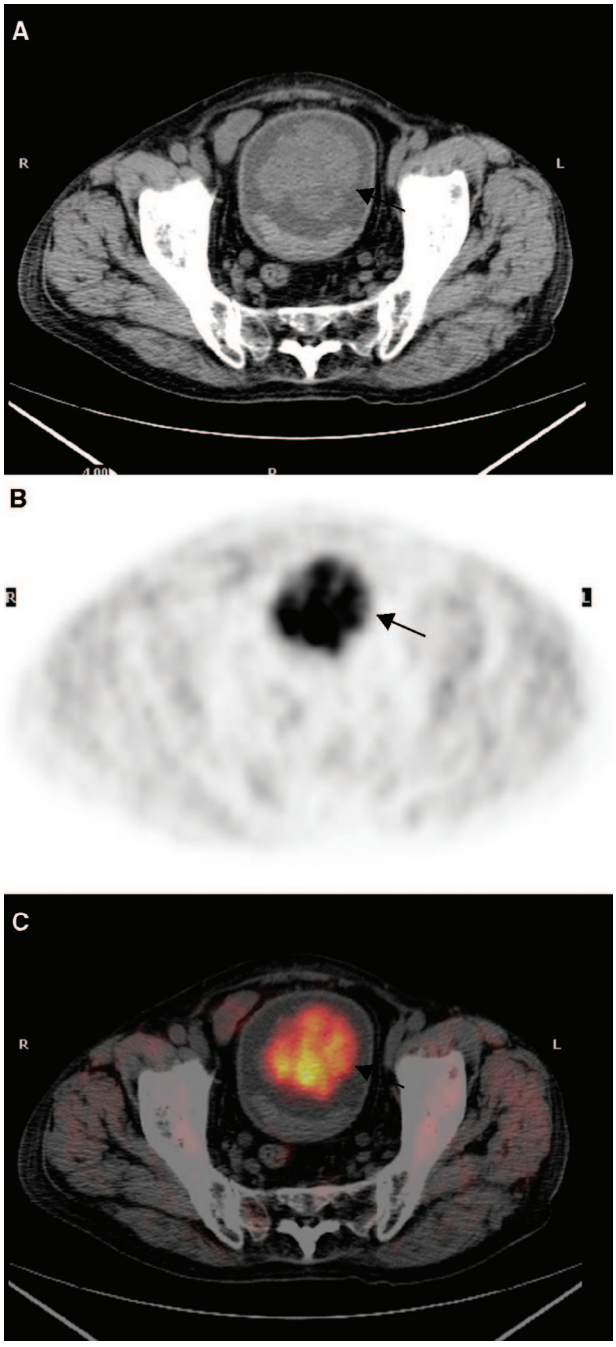

FIGURE 1. C-11 choline PET/CT image of an 84-year-old patient with prostate cancer. CT transaxial image (**A**) shows enlarged prostate (arrow) protruding into the bladder. PET image (**B**) shows increased uptake of the radioactivity in the prostate (arrow). PET/CT transaxial image (**C**) shows diffuse accumulation of the radioactivity in the entire prostate gland (arrow).

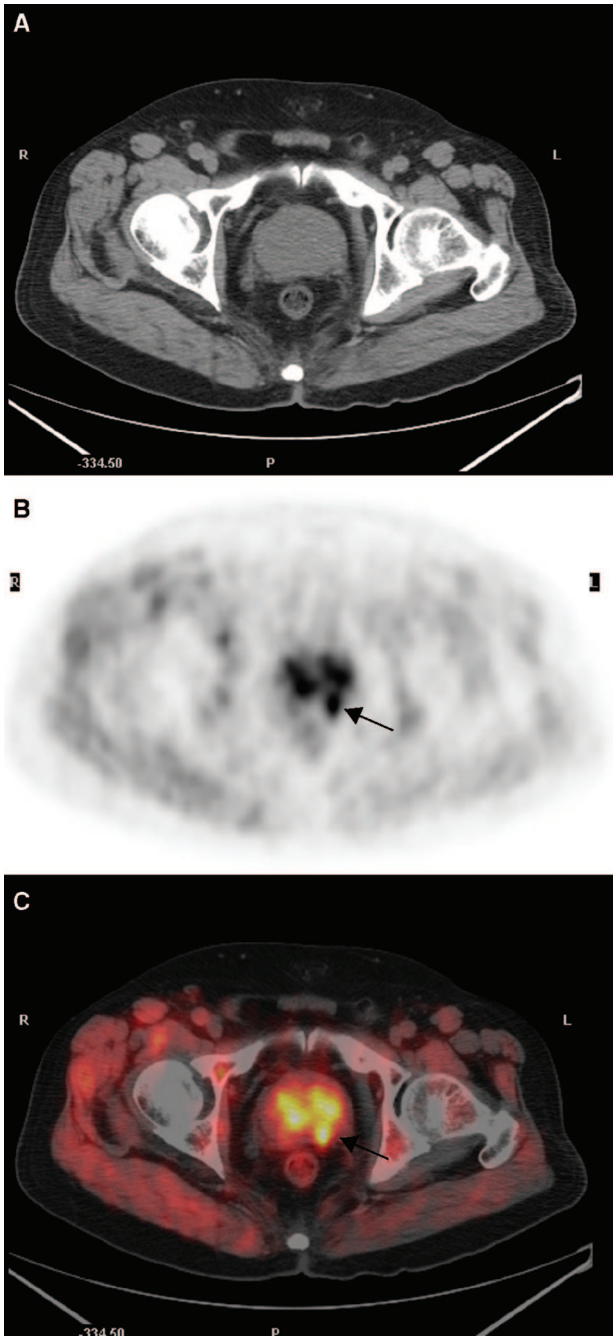

FIGURE 2. C-11 choline transaxial PET/CT image of a 78-year-old patient with prostate cancer. CT image (**A**) shows a little protrusion in the left lobe. PET image (**B**) shows a hot spot in the left lobe (black arrow). PET/CT image (**C**) shows the hot spot in the nodule protruding from the normal left lobe of the prostate (arrow).

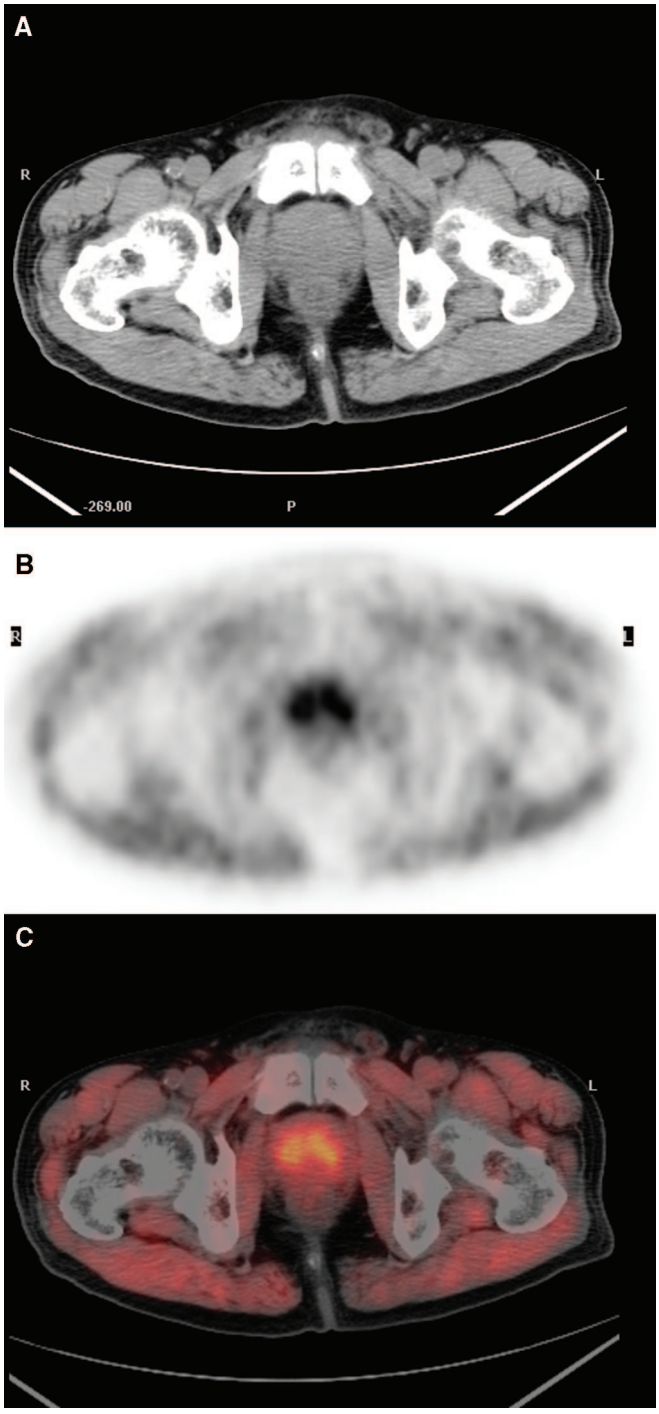

FIGURE 3. C-11 choline transaxial PET/CT image of a 70-year-old patient with BPH (PSA 5.42 μg/L). CT image (**A**) shows no abnormal nodule of the enlarged prostate. **B**, Shows symmetrical uptake of radioactivity in prostate. PET/CT image (**C**) shows symmetrical accumulation of radioactivity within the central zone of prostate.

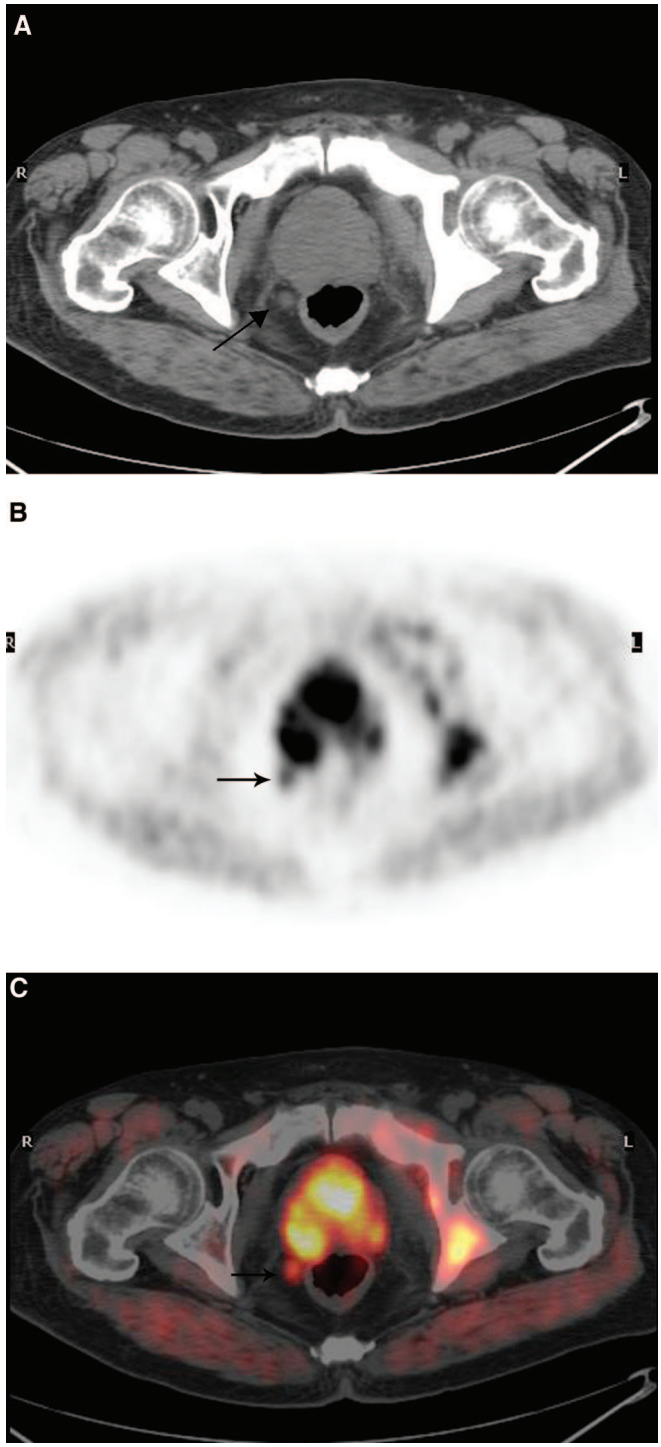

FIGURE 4. C-11 choline transaxial PET/CT image of an 81-year-old patient with prostate cancer with lymph node and bone metastases. CT image (**A**) shows a pelvic lymph node (diameter = 1cm) right behind the prostate (arrow). PET image (**B**) shows high radioactivity in the prostate region and a small hot spot (arrow) right behind it and irregular high uptake in the left. PET/CT image (**C**) shows increased activity in the prostate and a small hot spot in the pelvic lymph node (arrow). The irregular avid accumulation is located in the left ischium.

and 4.95 ± 5.14 (0.89–27.93) without a statistically significant difference ($t = 2.02$; $P > 0.05$). No significant correlations were observed between SUVmax, age, PSA, and Gleason score.

Using P/M as a Semiquantitative Parameter. In the PCa group, the mean values and ranges of SUVmean and SUVmax in the muscle were 1.62 ± 0.72 (0.93–3.55), 1.8 ± 0.76 (0.98–3.91). However, in the BPH group, the mean values and ranges of SUVmean and SUVmax in muscle were 2.19 ± 2.32 (0.82–13.52), 2.4 ± 2.42 (0.89–14.19). The ratio of the SUVmax of the prostate lesion to that of muscle was calculated. The mean values and ranges of P/M of the PCa and BPH were 4.21 ± 1.61 (1.85–7.82) and 1.87 ± 0.98 (0.69–5.04), respectively, with a significant difference ($t = 2.04$; $P < 0.01$).

ROC Curve. The ROC curve was created by SPSS using P/M of all patients enrolled. The area under the ROC curve for diagnosing PCa upon P/M was 0.918. The threshold P/M of 2.3 was chosen to yield the maximal accuracy. Using this criterion for differentiating malignant from benign lesions, of the 23 patients with positive PET/CT findings, 19 were proven as PCa histologically, whereas the remaining 4 patients were BPH, including 1 BPH accompanied by chronic prostatitis (P/M was 4.54, 2.41, 5.04, 2.64). Of 26 patients with negative PET/CT results, 24 were BPH (true-negative), 1 was well-differentiated adenocarcinoma, and 1 was poorly differentiated adenocarcinoma (P/M and size were 1.85, 1.5 × 1.2 cm, 1.91, 1.0 × 0.8cm, respectively). The overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of C-11 choline PET/CT in the detection of PCa were 90.48% (19 of 21), 85.71% (24 of 28), 82.61% (19 of 23), 92.31% (24 of 26), and 87.76% (43 of 49).

DISCUSSION

Recent studies have assessed the role of C-11 choline PET for localization and detection of PCa and show controversial results.[1,2,7,10,11] Because previous studies included a small number of patients with BPH, this study covered 28 patients with BPH and 21 PCas who underwent C-11 choline PET/CT in our center for about 2 years. The results indicate that the difference between SUVmax of the PCa and BPH was not statistically significant (7.87 ± 5.74, 4.95 ± 5.14, respectively, $t = 2.02$, $P > 0.05$). During the analysis of the imaging phenomena, it was found that in 1 patient with BPH, the SUVmax of the prostate lesions was 27.93, whereas that of muscle was as high as 14.19, and the SUVmax of muscle in some patients was more than 3. In addition, the ratio of both measurements might cancel out a general factor affecting SUV measurement (ie, time of acquisition, measurement of activity). Thus, we presume that P/M might be more meaningful than SUVmax in differentiating malignant tumors from benign disease. P/M in all patients was calculated and subsequent results showed that there was a significant statistical difference in P/M between PCa and BPH (4.21 ± 1.61, 1.87 ± 0.98, respectively, $t = 2.04$, $P < 0.01$). The background of the increased uptake of choline in muscle of some patients is not completely understood and the exact reasons need further investigated.

The analysis of Wachter et al[12] demonstrated the necessity of combining the advantage of exact anatomic information derived from conventional imaging with the improved tumor information derived from functional PET imaging. In this study, 4 slices of a helical CT scan and imaging parameters (WW 350Hu, WL 35Hu) could manifest the prostate gland clearly. In addition, drinking water to fill the bladder could result in a liquid density area in the bladder, which can contribute to observing the protruded prostate gland. By providing more precise anatomic information of a small lesion, the visualization of PET/CT may be helpful in distinguishing accumulation of radioactivity in the peripheral zone where most PCa occurred from the central zone where BPH commonly occurred. In false positive cases, all sites of elevated radioactivity were in the central zone and shown as hot spots symmetrically. It showed that symmetrical accumulation of activity in the central zone probably means BPH, whereas a hot spot in the peripheral zone indicates PCa. Of course, we should emphasize that, although focal uptake in the peripheral zone is associated with a diagnosis of PCa, diffuse tracer accumulation in the whole gland made PCa more likely, which could be diagnosed easily. The 2 false negative cases indicated that C-11 choline PET/CT could have false negative results in a well-differentiated and small size tumor.

CONCLUSION

C-11 choline PET/CT is a valuable noninvasive imaging technology in the diagnosis of PCa, particularly in patients with increased PSA levels. To differentiate PCa from benign lesions, the parameter P/M is better than SUV, but an appropriate criterion still needs further investigation. C-11 choline is avidly taken up in both PCa and BPH, but the precise localization of PET/CT could offer a great deal of assistance. The symmetrical accumulation within the central zone of the prostate probably indicates BPH, whereas a hot spot within the peripheral zone of the prostate gland suggests a high risk of PCa.

REFERENCES

1. Scher B, Seitz M, Albinger W, et al. Value of C-11 choline PET and PET/CT in patients with suspected prostate cancer. *Eur J Nucl Med Mol Imaging*. 2007;34:45–53.
2. Reske SN, Blumstein NM, Neumaier B, et al. Imaging prostate cancer with ^{11}C-choline PET/CT. *J Nucl Med*. 2006;47:1249–1254.
3. Lawrentschuk N, Davis ID, Bolton DM, et al. Positron emission tomography and molecular imaging of the prostate: an update. *BJU Int*. 2006;97:923–931.
4. Rodriguez-González A, Molina AR, Fernández F, et al. Inhibition of choline kinase as a specific cytotoxic strategy in oncogene-transformed cells. *Oncogene*. 2003;22:8803–8812.
5. Heinisch M, Dirisamer A, Loidl W, et al. Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA <5 ng/ml? *Mol Imaging Biol*. 2006;8:43–48.
6. Breeuwsma AJ, Pruim J, Jongen MM, et al. In vivo uptake of [^{11}C]choline does not correlate with cell proliferation in human prostate cancer. *Eur J Nucl Med Mol Imaging*. 2005;32:668–673.

7. Sutinen E, Nurmi M, Roivainen A, et al. Kinetics of [^{11}C]choline uptake in prostate cancer: a PET study. *Eur J Nucl Med Mol Imaging*. 2004; 31:317–324.
8. Fazio F, Picchio M, Messa C. Is ^{11}C-choline the most appropriate tracer for prostate cancer? For. *Eur J Nucl Med Mol Imaging*. 2004;31:753–756.
9. Zophel K, Kotzerke J. Is ^{11}C-choline the most appropriate tracer for prostate cancer? Against. *Eur J Nucl Med Mol Imaging*. 2004;31:756–759.
10. Yoshida S, Nakagomi K, Goto S, et al. ^{11}C-choline positron emission tomography in prostate cancer: primary staging and recurrent site staging. *Urol Int*. 2005;74:214–220.
11. Martorana G, Schiavina R, Corti B, et al. ^{11}C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. *J Urol*. 2006;176: 954–960.
12. Wachter S, Tomek S, Kurtaran A, et al. ^{11}C-acetate positron emission tomography imaging and image fusion with computed tomography and magnetic resonance imaging in patients with recurrent prostate cancer. *J Clin Oncol*. 2006;24:2513–2519.